PATENT
Attorney Docket No. 04249.0002-04000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| In re Application of: | ) | |
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| SULLIVAN et al. | ) | |
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| Serial No.: 08/277,288 | ) | Group Art Unit: 1806 |
| | ) | |
| Filed: July 22, 1994 | ) | Examiner: R. Schwadron |
| | ) | |
| For: ANTIBODY PURIFICATION PROCESS | ) | |

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

**DECLARATION OF DR. DAMON SMITH UNDER 37 C.F.R. § 1.132**

I, **DAMON SMITH, Ph.D.,** hereby declare as follows:

1. I am a citizen of the United Kingdom and a resident of 7 Castle Road, Colchester, Essex, CO1 IUW, UK.

2. I received my Ph.D. degree in Biochemistry from the University of Essex, Wivenhoe Park, Colchester.

3. I have done a Postdoctoral Research Fellowship at St. Georges Hospital, London, where I was involved in immunological research related to Alzheimer's disease. Antisera were raised to normal and abnormal forms of a protein found in the Alzheimer's patients.

4. During the last several years my research has involved raising polyclonal antibodies to a variety of antigens. I also designed peptide antigens for distinguishing isomeric forms of proteins, as well as identifying the remnants of proteins

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altered in disease states. As such, I have been actively involved in the fields of immunology and immunotherapeutic therapy.

5. As a Group leader at Therapeutic Antibodies, Inc., I have personally been responsible for directing a group of scientists involved in developing novel antivenoms for a number of snake species.

6. Venoms comprise several proteins in the molecular weight range of 20,000 to 90,000 daltons and, when complexed with a F(ab) fragment, would be too large to be excreted rapidly by glomerular filtration.

7. Antivenins comprising intact antibodies have been sold commercially since at least 1947. Antivenins comprising $F(ab)_2$ fragments have been sold commercially since at least 1969. No significant improvements have been made to commercial antivenins since 1969.

8. Digoxin is a small molecule that is ingested and dispersed in the bloodstream and interstitial fluid. Snake venoms are large hydrophobic molecules that are injected into the muscle or fatty tissues and slowly released from the site of the bite. Because F(ab) is cleared rapidly, one might have expected that a single administration of F(ab) antivenin would not effectively neutralize later-released venom.

9. $F(ab)_2$ fragments and intact antibodies have two binding sites, whereas F(ab) fragments have only a single binding site. As a result, F(ab) fragments cannot form cross-linked antibody-antigen complexes like F(ab) fragments and

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intact antibodies or initiate complement fixation like such complexes. Formation of such complexes is important to their removal by the reticuloendothelial system, where large complexes are cleared most quickly.

10. Because F(ab) fragments are relatively small (compared to intact immunoglobulins and F(ab) fragments) and venom molecules are relatively large (compared to digoxin), one skilled in the art would have been concerned that a F(ab)-venom complex would retain toxicity.

11. Paragraphs 12 and 13 describe a clinical study in which patients have been treated with TAb001, a purified ovine F(ab) fragment for treating Vipera berus envenoming, and compared to patients treated with a convention $F(ab)_2$ antivenin.

12. Methods

A multicenter study was set up in Sweden in 1991 to assess the efficacy and safety of TAb001, a venom-specific affinity purified antivenom, in patients with moderate-severe Vipera berus envenoming. The criteria for inclusion in the trial were: (i) circulatory failure responding poorly to symptomatic treatment or recurring; (ii) protracted or recurrent gastrointestinal symptoms; or (iii) less severe circulatory disturbances or rapidly progressing local edema with any of the following -- pronounced leucocytosis; extensive hemolysis, coagulopathy; metabolic acidosis; increased serum activity of creatine kinase; or electrocardiographic changes. Eighteen patients were entered into the study. All patients were monitored according to a protocol describing clinical and

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laboratory procedures to be followed throughout their inpatient stay and at follow-up on three occasions during the month after discharge. Two earlier reported patient groups with a similar degree of envenoming were used as control groups for evaluation of treatment efficacy. In one of these groups, consisting of sixteen patients, no antivenom was given, whereas in the other group, including thirty patients, an equine $F(ab)_2$ antivenom was used in a dose of 1.4 g.

The first four patients received 100 mg of TAb001 administered via i.v. infusion over 30 minutes. The dose was then increased to 200 mg to determine if a higher dose could further reduce the incidence of progressive swelling associated with Vipera berus bites.

13. Results

The Results are presented in the following Table:

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**TABLE**

| Parameter | Type of Antivenom Treatment: No Antivenom (n = 16)[1/] | Conventional (n = 30)[2/] | TAb001 (n = 18) |
|---|---|---|---|
| Average Hospital Median Stay (Days) | 6 | 3 | 3 |
| Extensive Edema Involving Trunk | 88% | 23% | 17% |
| Pronounced Anemia (>10% below normal lower limit) | 44% | 10% | 17% |
| Associated Allergic Side Effects | \ | 10% | None |

Previous experience[1/2/] suggests that the most suitable parameters for evaluating the outcome of antivenom treatment are the development of edema, anemia and the duration of hospital stay. These features were studied in patients treated with TAb001 and compared with the corresponding parameters in patients treated with either conventional antivenoms or no antivenom. TAb001 appears to be equally effective as the conventional antivenom in reducing the occurrence of extensive edema and severe anemia as well as shortening hospital stay. Moreover, to date, no allergic events, suggesting an immediate or delayed hypersensitivity response, have been observed after administration of TAb001, whereas 10% of those given conventional antivenom had allergic side-effects.

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1/ Persson, H., and Irestedt, B., "A study of 136 cases of adder bite treated in Swedish hospitals during one year," Acta Med. Scand., 210: 433-9 (1981).

2/ Karlson-Stiber, C., and Persson, H., "Antivenom treatment in 30 cases of Vipera berus envenomation in Sweden 1985-1989," Br. Med. J. Submitted for publication.

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14. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Damon Smith, Ph.D

Signed on this 20th day of December, 1994

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